Studies Directed toward a Total Synthesis of Nucleoside Q. The Annulation of 2,6-Diaminopyrimidin-4-one with α-Halo Carbonyls to Form Pyrrolo[2,3-*d*]pyrimidines and Furo[2,3-*d*]pyrimidines

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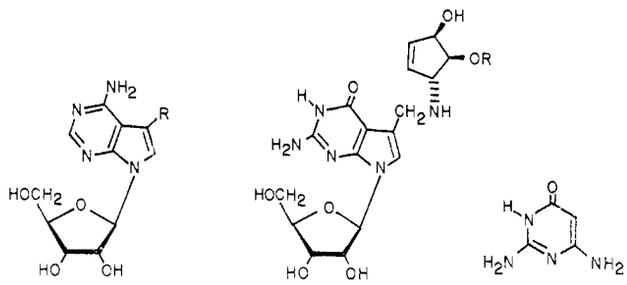
The condensation of 2,6-diaminopyrimidin-4-one (**3**) with various α-halo carbonyl compounds is examined. The reaction produces two types of products, both regiospecifically. For example, treatment of **3** with α-chloroacetone affords 2-amino-6-methylpyrrolo[2,3-*d*]pyrimidin-4-one (**5a**) and 2,4-diamino-5-methylfuro[2,3-*d*]pyrimidine (**6a**). Depending upon the nature of the α-halo carbonyl compound, pyrrolo[2,3-*d*]pyrimidin-4-one and/or furo[2,3-*d*]pyrimidine products were observed. Structural assignments were based on UV, ^{1}H NMR, and ^{13}C NMR. 2-Chloropropionaldehyde was found to react with **3** to produce 2-amino-5-methylpyrrolo[2,3-*d*]pyrimidin-4-one (**7**) exclusively, thus providing an entry into the substitution pattern of nucleoside Q (**2**).

The pyrrolo[2,3-*d*]pyrimidine ring system has aroused considerable interest due to its presence in several natural products. It is contained in the nucleoside antibiotics tubercidin (**1a**), toyocamycin (**1b**), and sangivamycin (**1c**),[2] as well as in the more recently characterized hypermodified nucleosides Q (**2a**)[3] and Q* (**2b** and **2c**).[4] Both Q and Q* are present in the initial position of the anticodon in tyrosine, aspartate, asparagine, and histidine tRNA from various organisms.[5]



1: **a**, R = H; **b**, R = CN; **c**, R = $CONH_2$

2: **a**, R = H; **b**, R = β-D-galactosyl or **c**, β-D-mannosyl

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Since Q in that position may not have a major effect on protein synthesis, a regulatory function has been suggested, though no definitive evidence is yet available. Interest in Q and its biological properties, coupled with its unique structure (it is the only skeletally modified nucleoside thus far isolated from RNA) and lack of availability in quantity, have prompted several groups to direct efforts toward its synthesis,[6-11] with one success reported thus far.[12] General entry into the pyrrolo[2,3-*d*]pyrimidine system has been achieved (a) from pyrrole-based precursors by formation of the pyrimidine ring,[13-15] (b) from pyrimidines with a 5-acetaldehyde or acetone side chain and adjacent amino group by cyclization with acid,[16-18] (c) from 4-pyrimidinylhydrazones by a thermally induced reaction analogous to the Fischer indole synthesis,[19,20] and (d) by condensation of 2-amino-6-alkylamino-4-hydroxypyrimidines, 6-aminouracil, and several other related compounds with aqueous chloroacetaldehyde.[16,21] The only approaches that have been utilized specifically for the 7-deazaguanine system contained in nucleoside Q are (b)[6,9,12] and the modification of the intact pyrrolo[2,3-*d*]pyrimidine ring in tubercidin and toyocamycin.[7,8]

Our strategy, based on the chloroacetaldehyde precedent, was to build the pyrrole ring onto a preformed pyrimidine ring, thus generating the 7-deazaguanine ring directly. By employing the appropriate α-halo carbonyl compound, substituents might be introduced into the pyrrole ring, later to be elaborated to the side chain of Q. Specifically, we present the initial results of our investigation of the reactions of various α-halo carbonyls with 2,6-diamino-4-pyrimidinone (**3**). We have determined the sites of attack, the major products, and the regiochemistry of the reaction.

Results and Discussion

In principle, an α-halo carbonyl compound might annulate **3** in a variety of ways. In addition to the aforementioned precedent for pyrrolo[2,3-*d*]pyrimidine formation, chloroacetaldehyde is well known to condense at two nitrogens to form a fused imidazo ring, as seen in its reactions with cytosine and adenine-containing moieties.[22] No precedent for the formation of a furo[2,3-*d*]pyrimidine by this route exists to our knowledge, though thieno[2,3-*d*]pyrimidines are formed with a 4-thio substituent present.[23]

Chloroacetone was chosen as the initial substrate, and proved to be representative of all the α-halo ketones that we examined. Stirring an excess of α-chloroacetone with **3** in DMF at 55 °C for 2 days afforded two products, **5a** (55%) and **6a** (20%), which were readily separated chromatographically. Other solvents gave the same two products, but DMF in general resulted in superior yields under more moderate conditions. That both products were the result of condensation at C-5 of the pyrimidine is easily determined from the ^{1}H NMR spectra, in which both **5a** and **6a** had only one vinyl proton; annulation by any other mode would produce two vinyl protons. A comparison of the ultraviolet spectra of **5a** and **6a** is presented in Figure 1. Though they are similar, the additional peak at 300 nm in the spectrum of **6a** in acid indicates that the two compounds have different chromophores. **5a** has UV, ^{1}H NMR, and ^{13}C NMR characteristics which readily allow assignment of the pyrrolo[2,3-*d*]pyrimidine system to it. However, depending upon the regiospecificity of the reaction, either the 5-methyl or the 6-methyl compound might be produced. Resolution of this question was possible via ^{13}C NMR data (Table II). The signal for C-6 (δ 126.1) remained a singlet during off-resonance decoupling, while C-5 (δ 98.5) split into a doublet, thus placing the methyl group at C-6. Also, **5a** has been prepared elsewhere by a different route,[6] and spectral data, including ^{13}C NMR resonances, are virtually identical. That the minor product is not the isomeric pyrrolo[2,3-*d*]pyrimidine is conclusively demonstrated by the UV spectrum, the presence of two groups of exchangeable protons (2 H each) at δ 6.2 and 6.4 in the ^{1}H NMR spectrum, and the dramatic differences in the ^{13}C NMR, to be discussed shortly. Also, in the ^{1}H NMR spectrum, the vinyl proton of **6a** occurs at δ 7.17, while for **5a** its chemical shift is δ 5.86. Thus, **6a** must be a furo[2,3-*d*]pyrimidine, since only one other direction of cyclization is possible. The question of the position

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Table I. Products from α-Halo Ketone Condensations with 3

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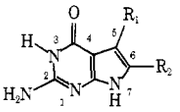

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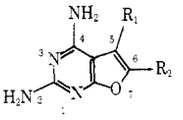

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	4	5	6
a	R_1 = H; R_2 = CH_3; X = Cl	R_1 = H; R_2 = CH_3	R_1 = CH_3; R_2 = H
b	R_1 = H; R_2 = $CH_2CO_2CH_2CH_3$; X = Br	R_1 = H; R_2 = $CH_2CO_2CH_2CH_3$	
c	R_1 = R_2 = CH_3; X = Br	R_1 = R_2 = CH_3	R_1 = R_2 = CH_3
d	R_1 = CH_3; R_2 = C_6H_5; X = Br	R_1 = CH_3; R_2 = C_6H_5	
e	R_1 = C_6H_5; R_2 = CH_3; X = Br	R_1 = C_6H_5; R_2 = CH_3	
f	R_1 = $CH_2C_6H_5$; R_2 = CH_3; X = Br	R_1 = $CH_2C_6H_5$; R_2 = CH_3	
g	R_1 = H; R_2 = CH_2Cl; X = Cl		R_1 = CH_2Cl; R_2 = H
h	R_1, R_2 = $-(CH_2)_4-$; X = Cl		R_1, R_2 = $-(CH_2)_4-$

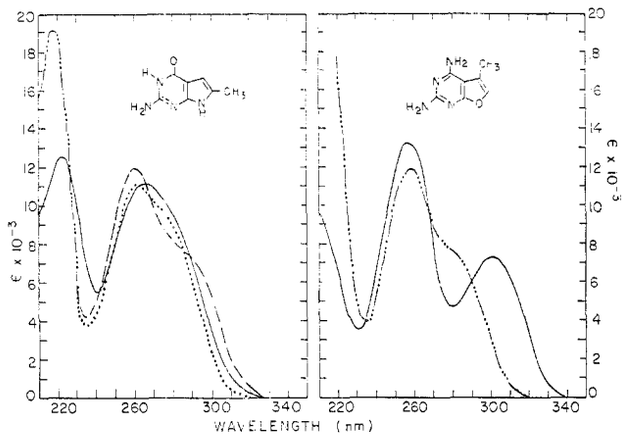


Figure 1. Ultraviolet absorption spectra of **5a** and **6a**: acid, —; pH 7, - - -; base, • • •.

of the methyl group is again readily resolved via the ^{13}C NMR spectrum (Table III), where C-5 (δ 93.0) remains as a singlet upon off-resonance decoupling, while C-6 (δ 133.4) splits into a doublet, thus placing the methyl at C-5 in **6a.**

Compound **5a** was initially isolated as the hydrochloride salt, and comparison of the ^{13}C NMR spectra of the neutral and protonated species (Table II) allows some conclusions to be drawn about the site of protonation. It has been observed that protonation (or alkylation) of a ring nitrogen will cause an upfield shift in the resonances of the adjacent carbons.[24-26] The large upfield shift of C-7a (13.6 ppm), together with the smaller upfield shifts of C-2 (1.5 ppm) and C-4 (2.6 ppm), make it likely that the major site of protonation in **5a** is N-1, with perhaps N-3 protonating to a much lesser extent. Conversion of **5a**·HCl to the free base was readily accomplished by stirring with Amberlite IR-45 (OH^- form).

A comparison of the ^{13}C NMR spectra of **5a** and **6a** (Tables II and III), which are indicative of other compounds prepared in this study, shows that resonances for C-2, C-4a, C-6, and C-7a all are considerably shifted downfield in **6a,** relative to **5a.** The outstanding characteristic, however, is certainly the position of C-7a at δ 169.4 in **6a** vs. δ 151.2 in **5a.** This signal, together with the aforementioned UV and ^1H NMR differences, allow facile assignment of each ring system for the other condensation reactions that we have examined.

For the series of α-halo ketones (**4a–h**) that we have examined, the products in all cases are pyrrolo[2,3-*d*]pyrimidines (**5**) and/or furo[2,3-*d*]pyrimidines (**6**) with substitution at C-5 and C-6 consistent with the pattern set forth in the chloroacetone case. The α-halo ketones and products are listed in Table I. Interestingly, ethyl 4-bromo-3-oxobutanoate (**4b**), 2-bromo-1-phenyl-1-propanone (**4d**), 1-bromo-1-phenyl-2-propanone (**4e**), and 3-bromo-4-phenyl-2-butanone (**4f**) give exclusively pyrrolo[2,3-*d*]pyrimidines, while 1,3-dichloroacetone (**4g**) and 2-chlorocyclohexanone (**4h**) afford only furo[2,3-*d*]pyrimidines. Chloroacetone (**4a**) and 2-bromo-3-butanone (**4c**) provide a mixture of the two ring systems. In order to contrast directly the change on going from a bromo to a chloro, 1-chloro-1-phenyl-2-propanone was also examined and was found to give substantially the same result as bromo compound **4e,** but at a much slower rate. In the cases (**5d** and **5e**) where the products differed only by the interchange of the methyl and phenyl at C-5 and C-6, ^{13}C NMR was utilized for positive structure identification. A phenyl substituent is known generally to cause a larger downfield shift in the carbon to which it is attached than a methyl group. Employing the dimethyl derivative **5c** for comparison purposes, C-5 in **5e** is 6.8 ppm downfield from C-5 in **5c,** while C-5 in **5d** is only 2.6 ppm downfield from C-5 in **5c.** This observation supports the structure expected based on the typical mode of addition. The same observation (in the reverse sense) applies to C-6 of **5d,** and hence it must be the positional isomer, as expected.

As has been alluded to earlier, the annulation reactions occur in a regiospecific manner. In cases where pyrrolo[2,3-*d*]pyrimidines are formed, the carbonyl carbon of the halo ketone becomes bonded to the 6-NH_2 of **3,** and the carbon attached to halogen is linked to C-5 of **3.** Furo[2,3-*d*]pyrimidine products are formed by bonding of the carbonyl carbon of the halo ketone to C-5 of **3,** with the carbon attached to halogen residing next to the oxygen at C-4 of **3.**

A variety of mechanistic possibilities exist to account for the bifurcate reaction of **3** and several precedents are worth mentioning. In the study where thieno[2,3-*d*]pyrimidines were isolated in a similar reaction, it was possible to adjust the conditions such that an S-alkylated intermediate was isolated.[23] In cases where a 5-acetaldehyde or 5-acetonyl side chain on a pyrimidine ring is cyclized to a furo[2,3-*d*]pyrimidine (via adjacent hydroxyl) or to a pyrrolo[2,3-*d*[pyrimidine (via adjacent amino), acidic conditions have been utilized.[16-18,27] For several reactions where aminopyrimidines annulate from nitrogen to nitrogen to form a fused imidazole ring, the carbonyl of the α-halo carbonyl becomes bonded to the exocyclic amino and the halogen-containing carbon to a ring nitrogen.[28-31] In a recent study kinetic evidence is presented to indicate that initial reaction occurs between the 6-amino of adenosine 5′-monophosphate and the carbonyl carbon of chloroacetaldehyde, followed by cyclization and loss of water.[32] Condensations involving β-dicarbonyls and aminopyrimidines, however, have been suggested to involve initial acylation at C-5 of the pyrimidine followed by ring closure.[33] The mechanisms leading to **5** and **6** must involve at least three major steps (not necessarily in this order): (1) bond formation between a heteroatom (O or N) of **3** and a carbon of the α-halo ketone, (2) bond formation between C-5 of **3** and a carbon of the α-halo ketone, and (3) loss of water. Additional steps would most likely be just prototropic shifts. Since under the reaction conditions employed no intermediates were isolated or were visible by thin-layer chromatographic analysis, no direct evidence is available.

Table II. ^{13}C Data for Pyrrolo[2,3-*d*]pyrimidines[a,b]

compd	registry no.	C_2	C_4	C_{4a}	C_5	C_6	C_{7a}	other carbons
5a	62981-82-2	152.2	158.7	99.8	98.5(d)	126.1	151.2	12.9 (CH_3, q)
5a (lit.[6])		151.8	158.4	99.9	98.6(d)	126.2	151.1	12.6 (CH_3, q)
5a·HCl	67194-80-3	150.7	156.1	100.1	99.9(d)	128.6	137.6	12.6 (CH_3, q)
5b	67226-39-5	152.0	158.5	99.8	100.6(d)	123.0	151.2	14.0 (CH_3, q), 33.1 (CH_2C=O, t), 60.3 (CH_2O, t), 170.0 (C=O)
5c	67194-81-4	151.1	158.3	99.4	108.1	122.1	145.6	9.4, 10.0 (2 CH_3, q)
5d	67194-82-5	152.4	159.6	100.9	110.7	125.7	151.2	11.2 (CH_3, q), 123.8 (d), 126.5 (d), 128.4 (d), 132.7 (aromatic)
5e	67194-83-6	151.7	158.0	97.6	114.9	123.6	148.6	11.5 (CH_3, q), 125.1 (d), 127.2 (d), 129.8 (d), 134.5 (aromatic)
5f	67226-40-8	151.6	158.9	98.8	111.8	122.1	149.9	10.4 (CH_3, q), 29.7 (CH_2, t), 125.0 (d), 127.9 (d), 128.2 (d), 142.7 (aromatic)
7	65062-57-9	152.1	159.4	99.4	112.9	113.5(d)	150.9	11.3 (CH_3, q)

[a] All resonances in ppm downfield from internal Me_4Si in Me_2SO-d_6. Letters in parentheses refer to multiplicities in off-resonance decoupled spectra. In cases where no multiplicity is shown, the resonance remained a singlet. [b] It is possible that certain assignments may be reversed in cases where resonances occur in close proximity and the multiplicities are identical.

Table III. ^{13}C Data for Furo[2,3-*d*]pyrimidines[a,b]

compd	registry no.	C_2	C_4	C_{4a}	C_5	C_6	C_{7a}	other carbons
6a	67194-84-7	161.1	159.2	114.3	93.0	133.4(d)	169.4	9.7 (CH_3, q)
6c	67194-85-8	160.2	158.4	107.8	93.9	141.3	167.8	9.4 CH_3, q), 10.6 (CH_3, q)
6g	67194-86-9	157.7	155.5	117.3	90.7	137.9(d)	169.3	37.0 (CH_2Cl, t)
6h	67194-87-0	158.3	156.3	110.9	92.6	145.3	168.0	21.05 (t), 21.97 (t), 22.12 (t) (tetramethylene bridge)

[a] All resonances in ppm downfield from internal Me_4Si in Me_2SO-d_6. Letters in parentheses refer to multiplicities in off-resonance decoupled spectra. In cases where no multiplicity is shown, the resonance remained a singlet. [b] It is possible that certain assignments may be reversed in cases where resonances occur in close proximity and the multiplicities are identical.

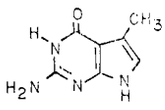
In an attempt to gain some insight into the general reaction, we have carried out some preliminary theoretical calculations on **3**.[34] The position of highest negative charge in the ground state is, in fact, N-6, while the atom with the highest electron density in the HOMO is C-5. In the electrophilic partner, the net positive charge and the coefficient of the LUMO of the carbonyl carbon of chloroacetone are considerably higher than the carbon attached to halogen. These calculations are consistent with the experimental data that we have gathered, though any firm conclusions will require calculation of the interaction energy as a function of the geometry of the possible transition states.

With regard to our overall goal of the synthesis of nucleoside Q and its free base, α-halo ketones thus do not provide the correctly substituted pyrrolo[2,3-*d*]pyrimidines. Two possibilities exist which might allow entry into the 7-substituted 7-deazaguanine system. First, if α-halo aldehydes will condense with **3** to produce pyrrolo[2,3-*d*]pyrimidines with the same regiochemistry as the α-halo ketones, then the correct substitution pattern would be available. Second, it has been reported that 5,6-dimethyl-4-aminofuro[2,3-*d*]pyrimidine when refluxed with concentrated hydrochloric acid will partially rearrange via opening of the furo ring to 5,6-dimethyl-4-hydroxypyrrolo[2,3-*d*]pyrimidine.[39] Thus, the 5-substituted furo[2,3-*d*]pyrimidines of this study might rearrange to 5-substituted pyrrolo[2,3-*d*]pyrimidines. Both possibilities were investigated.

Though **6c** readily rearranged partially to **5c** upon heating in aqueous HCl, when a proton was present at C-6 of the furo[2,3-*d*]pyrimidine (**6a** and **6g**), only decomposition was observed, presumably due to the instability of the open-chain intermediate under the reaction conditions.

As a prototype aldehyde, 2-chloropropionaldehyde was investigated. In most solvents, including DMF, the results did not look promising. However, in Me_2SO at ambient temperature a smooth reaction occurred to give the 5-methylpyrrolo[2,3-*d*]pyrimidine **7** in 60% yield. **7** was clearly distinct from **5a** and its spectral data (see Table II and the Experimental Section) were also confirmatory. Thus, the regiospecificity of the reaction type was preserved (no **5a** was formed). While neither 2,3-dichloropropionaldehyde nor 2,3-dibromopropionaldehyde reacted with **3** to give a clean product (decomposition products were obtained prior to condensation), other aldehydes have also exhibited the same reactivity to afford only pyrrolo[2,3-*d*]pyrimidines. Research utilizing this observation toward a facile total synthesis of Q is in progress and will be reported in due course.

That condensation of **3** with various α-halo carbonyls leads to pyrrolo[2,3-*d*]pyrimidines and/or furo[2,3-*d*]pyrimidines is interesting from several standpoints. The literature on cyclizations with α-halo carbonyls provides some information useful in understanding the chemistry. As mentioned earlier, several electron-rich pyrimidines (aside from **3**) react with chloroacetaldehyde to produce pyrrolo[2,3-*d*]pyrimidines. 1-Methylcytosine[40] and 4-amino-2,6-dimethoxypyrimidine[28] react with chloroacetaldehyde and α-bromoacetophenone, respectively, to form imidazo[1,2-*c*]pyrimidines (**8** from 1-methylcytosine, for example). Neither 4,6-diaminopyrimidine



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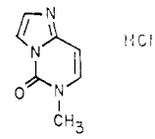

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nor 4-amino-6-pyrimidinone are reported to yield pyrrolo[2,3-*d*]pyrimidines with chloroacetaldehyde, though the nature of the products is not mentioned.[21] All of these data tend to indicate that there is a certain critical electron density (or HOMO coefficient) at C-5 which dictates whether cyclization will occur to that carbon or not, and **3** must exceed that minimum. The coupling of experimental observations with theoretical calculations might well provide a basis by which the direction (or directions) of cyclization of various pyrimidines with α-halo carbonyls could be predicted.[41]

Summary

The reaction of 2,6-diaminopyrimidin-4-one (**3**) with α-halo ketones proceeds via two distinct, regiospecific pathways, leading to 5-substituted and 5,6-disubstituted 2,4-diaminofuro[2,3-*d*]pyrimidines and/or 6-substituted and 5,6-disubstituted 2-aminopyrrolo[2,3-*d*]pyrimidin-4-ones. The former reaction provides a new and facile entry into the furo[2,3-*d*]pyrimidine system. The utilization of these 2,4-diaminofuropyrimidines and their derivatives as potential dihydrofolate reductase inhibitors (pteridine antagonists) has also been investigated and will be reported elsewhere. 2-Chloropropionaldehyde also reacts with **3** regiospecifically, forming only 2-amino-4-hydroxy-5-methylpyrrolo[2,3-*d*]pyrimidine (**7**). This observation allows convenient formation of the proper substitution pattern for nucleoside Q, and research toward its synthesis is currently in progress.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting-point apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer 467 grating infrared spectrophotometer. ^{1}H NMR spectra were measured with Varian A-60A or EM-360 instruments, and ^{13}C NMR spectra with a Bruker WP 80; chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Ultraviolet absorption spectra were recorded on a Cary 15 ultraviolet–visible spectrophotometer. Quantitative measurements were carried out by making a stock solution of the heterocycle in either H_2O (**5a, 5b, 6a, 6c, 6h, 7**) or CH_3OH (**5c–f, 6g**) and then diluting with either 0.1 N HCl, 0.1 N NaOH, pH 4.0 acetate buffer, or pH 7.0 phosphate buffer. Extinction coefficients are listed in parentheses. Mass spectra were recorded with an AEI-MS9 spectrometer at 70 eV. Microanalyses were done by Galbraith Laboratories, Inc. In all cases where analyses included methanol, the methyl protons were observed in the ^{1}H NMR spectra.

Reagent grade dimethylformamide was dried over molecular sieves and used directly. Dimethyl sulfoxide was distilled from calcium hydride.

Thin-layer chromatography was carried out on Eastman Chromagram sheets (silica gel) using the following systems: A, 9:1 $CHCl_3$–CH_3OH; B, 85:15 $CHCl_3$–CH_3OH; C, 4:1 $CHCl_3$–CH_3OH.

General Procedure for the Reaction of 2,6-Diaminopyrimidin-4-one (3) with α-Halo Ketones. To a suspension of **3** in DMF was added the α-halo ketone and the mixture was stirred (appropriate details are listed with each specific compound). The progress of the reactions was easily followed by TLC. Upon completion of the reaction, solvent was removed in vacuo. Purification was accomplished by column chromatography on silica gel.

2-Amino-6-methylpyrrolo[2,3-*d*]pyrimidin-4-one (5a) and 2,4-Diamino-5-methylfuro[2,3-*d*]pyrimidine (6a): 3 (0.5 g, 3.4 mmol), 1-chloro-2-propanone (**4a,** 0.37 g, 4 mmol), 6 mL of DMF; 50–60 °C; 2 days. Chromatography (2.5 × 38 cm column, elution with 9:1 $CHCl_3$–CH_3OH) afforded 300 mg of **5a** (55%, R_f 0.37, C) and 110 mg of **6a** (20%, R_f 0.56, C) as off-white solids. Recrystallization from methanol gave analytically pure materials. **5a** is initially isolated as the hydrochloride salt. Neutralization can be accomplished by stirring the salt 1 day at 80 °C with an excess of Amberlite IR-45 (OH^- form), followed by filtration and evaporation of solvent.

5a: mp (**5a**·HCl) >260 °C; ^{1}H NMR (**5a**·HCl, Me_2SO-d_6) δ 2.24 (s, 3, CH_3), 6.14 (s, 1, H_5), 6.6–9.0 (br m, 3, 3 NH), 11.66 (br s, 1, NHCO); ^{1}H NMR (**5a,** Me_2SO-d_6) δ 2.17 (s, 3, CH_3), 5.86 (s, 1, H_5), 6.27 (br s, 2, NH_2), 10.15 (br s, 1, NH), 10.80 (br s, 1, NH); MS *m/e* 164 (M^+, base), 163, 147, 135, 122; exact mass calcd *m/e* 164.0698; found *m/e* 164.0701; UV λ_{max} (acid) 222 (12 700), 264 (11 180); UV λ_{max} (pH 7.0) 217 (19 460), 260 (11 930), 280 (sh, 8050); UV λ_{max} (base) 260 (11 050).

Anal. Calcd for $C_7H_8N_4O$·HCl: C, 41.91; H, 4.52; N, 27.93. Found: C, 42.16; H, 4.81; N, 27.68.

6a: mp >260 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.28 (s, 3, CH_3), 6.10 (br s, 2, NH_2), 6.60 (br s, 2, NH_2), 7.17 (s, 1, H_6); MS *m/e* 164 (M^+, base), 149, 135, 122; exact mass calcd *m/e* 164.0698; found *m/e* 164.0701; UV λ_{max} (acid) 257 (13 380), 302 (7390); UV λ_{max} (pH 7.0) 215 (11 150), 258 (12 020), 280 (sh, 7650); UV λ_{max} (base) 257 (12 040), 275 (sh, 8080).

Anal. Calcd for $C_7H_8N_4O$: C, 51.21; H, 4.91; N, 34.13. Found: C, 50.84; H, 4.95; N, 33.77.

2-Amino-6-carboethoxymethylpyrrolo[2,3-*d*]pyrimidin-4-one (5b): 3 (1.44 g, 10 mmol), ethyl 4-bromo-3-oxobutyrate (**4b,** 2.1 g, 10 mmol), 15 mL of DMF; 50 °C; 12 h. Chromatography (3.8 × 60 cm column, elution with 92:8 $CHCl_3$–CH_3OH) afforded 1.40 g (60%, R_f 0.70, C) of a colorless solid. Recrystallization from methanol gave analytically pure material: mp >260 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.14 (t, 3, CH_3), 3.50 (s, 2, CH_2CO), 4.02 (q, 2, CH_2CH_3), 6.0 (s, 3, 2 NH, H_5), 10.12 (s, 1, NH), 10.80 (s, 1, NH); MS *m/e* 236 (M^+), 163 (base), 146, 121; exact mass calcd *m/e* 236.0909; found *m/e* 236.0915; UV λ_{max} (acid) 221 (14 440), 263 (12 020); UV λ_{max} (pH 7.0) 216 (18 530), 261 (13 730), 280 (sh, 9080); UV λ_{max} (base) 262 (11 500).

Anal. Calcd for $C_{10}H_{12}N_4O_3$: C, 50.84; H, 5.12; N, 23.72. Found: C, 50.68; H, 5.20; N, 23.64.

2-Amino-5,6-dimethylpyrrolo[2,3-*d*]pyrimidin-4-one (5c) and 2,4-Diamino-5,6-dimethylfuro[2,3-*d*]pyrimidine (6c): 3 (4.0 g, 28 mmol), 3-bromo-2-butanone (**4c,** 5.0 g, 33 mmol), 15 mL of DMF; 55 °C; 1 day. Chromatography (5 × 80 cm, elution with 9:1 $CHCl_3$–CH_3OH) afforded 2.1 g of slightly yellow **6c** (42%, R_f 0.64, B) and 2.2 g of slightly pink **5c** (44%, R_f 0.48, B). Recrystallization of both compounds from methanol gave analytically pure material.

5c: mp 227–238 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 2.10 (s, 6, 2 CH_3), 4.8–6.7 (br s, 3, 3 NH), 11.6 (s, 1, NHCO); MS *m/e* 178 (M^+, base), 177, 163, 149, 125; exact mass calcd *m/e* 178.0855; found *m/e* 178.0858; UV λ_{max} (acid) 229 (14 040), 272 (9920); UV λ_{max} (pH 7.0) 223 (17 990), 266 (9810), 283 (sh, 7880); UV λ_{max} (base) 266 (9070).

Anal. Calcd for $C_8H_{10}N_4O$·CH_3OH: C, 51.42; H, 6.71; N, 26.65. Found: C, 51.14; H, 6.67; N, 26.45.

6c: mp 175–185 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 2.10 (s, 3, CH_3), 2.16 (s, 3, CH_3), 3.8–5.5 (br s, 2, NH_2), 6.93 (br s, 2, NH_2); MS *m/e* 178 (M^+, base), 177, 163, 149, 135; exact mass calcd *m/e* 178.0855; found *m/e* 178.0858; UV λ_{max} (acid) 261 (14 830), 307 (7250); UV λ_{max} (pH 7.0) 259 (13 700), 280 (sh, 8580); UV λ_{max} (base) 259 (13 480).

Anal. Calcd for $C_8H_{10}N_4O$: C, 53.92; H, 5.66; N, 31.44. Found: C, 53.80; H, 5.74; N, 31.39.

2-Amino-5-methyl-6-phenylpyrrolo[2,3-*d*]pyrimidin-4-one (5d): 3 (2.90 g, 20 mmol), 2-bromo-1-phenyl-1-propanone (**4d,** 5.0 g, 23.5 mmol), 8 mL of DMF; 60 °C; 4 days. Chromatography (3.8 × 60 cm column, elution with 9:1 $CHCl_3$–CH_3OH) afforded 2.15 g of yellow **5d** (45%, R_f 0.49, A). Recrystallization from methanol provided analytically pure material: mp >260 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.40 (s, 3, CH_3), 6.09 (br s, 2, NH_2), 7.0–7.8 (m, 5, aromatic), 10.20 (br s, 1, NH), 11.08 (br s, 1, NHCO); MS *m/e* 240 (M^+, base), 239, 223, 206, 204; exact mass calcd *m/e* 240.1011; found *m/e* 240.1017; UV λ_{max} (acid) 230 (21 090), 290 (21 690); UV λ_{max} (pH 7.0) 227 (22 980), 297 (21 790); UV λ_{max} (base) 316 (22 000).

Anal. Calcd for $C_{13}H_{12}N_4O$·CH_3OH: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.69; H, 5.87; N, 20.83.

2-Amino-6-methyl-5-phenylpyrrolo[2,3-*d*]pyrimidin-4-one (5e): 3 (2.90 g, 20 mmol), 1-bromo-1-phenyl-2-propanone (**4e,** 4.30 g, 20 mmol), 20 mL of DMF; room temperature; 3 days. Chromatography (3.8 × 60 cm column, elution with 9:1 $CHCl_3$–CH_3OH) afforded 2.62 g of slightly violet-colored **5e** (54%, R_f 0.41, A). Recrystallization from methanol gave analytically pure material: mp >250 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.10 (s, 3, CH_3), 5.8–8.2 (br m, 8, aromatic, 3 NH), 11.14 (br s, 1, NHCO); MS *m/e* 240 (M^+, base), 239, 223, 205, 198; exact mass calcd *m/e* 240.1011; found *m/e* 240.1015; UV λ_{max} (acid) 235 (16 480), 254 (sh, 13 580), 275 (sh, 12 630); UV λ_{max} (pH 7.0) 234 (18 260), 264 (12 370), 297 (11 050); UV λ_{max} (base) 266 (11 800).

Anal. Calcd for $C_{13}H_{12}N_4O$: C, 64.99; H, 5.03; N, 23.32. Found: C, 65.01; H, 5.25; N, 23.39.

2-Amino-5-benzyl-6-methylpyrrolo[2,3-*d*]pyrimidin-4-one (5f): 3 (2.90 g, 20 mmol), 3-bromo-4-phenyl-2-butanone (**4f,** 4.50 g, 20 mmol), 20 mL of DMF; room temperature, 3 days. Chromatogra-

phy (3.8 × 60 cm column, elution with 9:1 $CHCl_3$–CH_3OH) afforded 1.90 g of white, crystalline **5f** (37%, R_f 0.38, A). Crystallization from methanol afforded analytically pure material: mp >250 °C; ^1H NMR (Me_2SO-d_6) δ 2.10 (s, 3, CH_3), 3.88 (s, 2, CH_2), 5.90 (s, 2, NH_2), 6.9–7.2 (m, 5, aromatic), 9.90 (br s, 1, NH), 10.48 (br s, 1, NHCO); MS *m/e* 254 (M^+, base), 253, 239, 177, 163, 139; exact mass calcd *m/e* 254.1168; found *m/e* 254.1175; UV λ_{max} (acid) 229 (16 320), 269 (11 650); UV λ_{max} (pH 7.0) 223 (20 880), 266 (11 480), 286 (sh, 8780); UV λ_{max} (base) 267 (10 870).

Anal. Calcd for $C_{14}H_{14}N_4O$·CH_3OH: C, 62.92; H, 6.34; N, 19.57. Found: C, 63.13; H, 6.22; N, 19.88.

5-Chloromethyl-2,4-diaminofuro[2,3-*d*]pyrimidine (6g): **3** (7.20 g, 50 mmol), 1,3-dichloroacetone (**4g**, 6.40 g, 50 mmol), 40 mL of DMF; room temperature; time 1 day. In this case filtration preceding removal of solvent under vacuum afforded 5.3 g of product. Chromatography of the residue from the filtrate (3.8 × 60 cm, elution with 9:1 $CHCl_3$–CH_3OH) afforded an additional 2.5 g of **6g**, total yield 78%, R_f 0.30, A. Recrystallization from methanol afforded analytically pure material: mp 178–188 °C dec; ^1H NMR (Me_2SO-d_6) δ 4.90 (s, 2, CH_2Cl), 6.12 (br s, 2, NH_2), 6.57 (br, s, 2, NH_2), 7.46 (s, 1, H_6); MS *m/e* 200, 198 (M^+, base), 163, 135, 121; exact mass calcd *m/e* 198.0308; found *m/e* 198.0312; UV λ_{max} (acid) 255 (10 420), 297 (5400); UV λ_{max} (pH 4.0) 259 (8560), 274 (sh, 6110); UV λ_{max} (pH 7.0) 215 (18 320), 278 (6590); UV λ_{max} (base) 259 (7440), 273 (sh, 6150).

Anal. Calcd for $C_7H_7N_4OCl$: C, 42.33; H, 3.55; N, 28.21. Found: C, 42.24; H, 3.63; N, 28.15.

2,4-Diamino-5,6-tetramethylenefuro[2,3-*d*]pyrimidine (6h): **3** (2.90 g, 20 mmol), 2-chlorocyclohexanone (**4h**, 2.70 g, 20 mmol), 20 mL of DMF; 60 °C; 3 days. Chromatography (3.8 × 60 cm column, elution with 9:1 $CHCl_3$–CH_3OH) afforded 1.73 g (43%) of colorless crystals. Recrystallization from methanol gave analytically pure material: mp >250 °C; ^1H NMR (Me_2SO-d_6) δ 1.60 and 2.40 (2 m, 8, 4 CH_2), 4.5–6.0 (br s, 2, NH_2), 6.67 (br s, 2, NH_2); MS *m/e* 204 (M^+, base), 203, 176, 161; exact mass calcd *m/e* 204.1011; found *m/e* 204.1017; UV λ_{max} (acid) 217 (14 100), 265 (13 650); UV λ_{max} (pH 7.0) 216 (20 570), 265 (13 580); UV λ_{max} (base) 261 (10 190).

Anal. Calcd for $C_{10}H_{12}N_4O$: C, 58.81; H, 5.92; N, 27.43. Found: C, 58.76; H, 6.01; N, 27.25.

2-Amino-5-methylpyrrolo[2,3-*d*]pyrimidin-4-one (7). A solution of 4.50 g (30 mmol) of **3**, 0.74 g (8 mmol) of 2-chloropropanal, and 10 mg of K_2CO_3 in 20 mL of Me_2SO was stirred at room temperature. After 1 and 2 h, identical proportions of aldehyde and K_2CO_3 were added. After a total of 4 h, 3 mL of 58% NH_4OH was added and the mixture chromatographed on silica gel (3.8 × 50 cm, elution with 600 mL of CH_2Cl_2, then 2 L of 85:15 CH_2Cl_2–CH_3OH) to afford 2.37 g (60%) of off-white crystals. Recrystallization from methanol gave analytically pure material: mp 198–210 °C dec; ^1H NMR (Me_2SO-d_6) δ 2.14 (s, 3, CH_3), 5.97 (s, 2, NH_2), 6.30 (s, 1, H_6), 10.10 and 10.56 (2 s, 2, 2 NH); MS *m/e* 164 (M^+, base), 163, 147, 122; exact mass calcd *m/e* 164.0698; found *m/e* 164.0701; UV λ_{max} (acid) 227 (14 690), 265 (8540); UV λ_{max} (pH 7.0) 223 (18 460), 262 (9060), 276 (sh, 7050); UV λ_{max} (base) 262 (7970).

Anal. Calcd for $C_7H_8N_4O$·$0.8CH_3OH$: C, 49.36; H, 5.95; N, 29.52. Found: C, 49.16; H, 6.04; N, 29.73.

Registry No.—**3**, 56-06-4; **4a**, 78-95-5; **4b**, 13176-46-0; **4c**, 814-75-5; **4d**, 2114-00-3; **4e**, 23022-83-5; **4f**, 55985-68-7; **4g**, 534-07-6; **4h**, 822-87-7.

References and Notes

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(34) All ab initio molecular orbital calculations were performed by the LCAO-MO-SCF method using the STO3G minimal basis set employing a modified version of the Gaussian 70 program.[35] Geometries were either taken from standard values[36] or from X-ray data for a closely related compound.[37] Gross atomic populations were calculated from the wave function by means of Mulliken's population analysis.[38] We thank Professor C. W. Kern and Dr. S. Nagase for helpful discussions.
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(41) Our preliminary calculations as described above indicate that an empirical correlation is possible, at least for the cases we have thus far examined. For example, 6-aminouracil exhibits the highest change density at 6-NH_2 and the highest HOMO coefficient at C_5, and cytosine has the highest charge density at the 4-NH_2 and the highest HOMO coefficient at N_3. For both of these cases, the data agree with the experimental observations.